American Academy of Dermatology

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Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Attention: ***Docket Number 78N-0038***
In Re: ***Sunscreen Monograph; Reopening of the Administrative Record***

Dear Sir or Madam:

The American Academy of Dermatology [hereinafter referred to as "the Academy"] submits these comments in response to the notice of reopening of the administrative record concerning the final monograph on sunscreens.

The Academy is the professional medical society for nearly 13,000 physicians specializing in diseases of the skin, hair, and nails. Dermatologists are the physicians most knowledgeable about and most likely to diagnose and treat skin cancers.

Solar exposure is an environmental issue with profound effects for the majority of Americans. In this century, changes in attitudes of most Americans toward fashion and beauty as well as an increase in leisure activity outdoors has cost us dearly in terms of photodamage, photoaging, and photocarcinogenesis. In the last decade, however, public health education programs have been initiated to try to convince the American public of the error of its ways. The Academy has led the way in this effort, engaged in the multimedia campaign to convince the public that unprotected sun exposure is dangerous and may lead to the development of melanoma and non-melanoma skin cancers, such as basal cell and squamous cell carcinoma.

This year, the American Academy of Dermatology estimates that 1.3 million Americans will be diagnosed with some form of skin cancer. The causal agent for the majority of these skin cancers is exposure to ultraviolet radiation (UVR). Genetic damage from UVR occurs in two general forms, mutations and chromosomal damage. Both are important to the development of the majority of neoplasms seen on the skin – both benign and malignant lesions. Exposure to UVR, especially in the ultraviolet B

(UVB) range of 290 to 320 nm, leads to mutations in the DNA by at least two potential mechanisms. In general, mutations arise in the skin when UV-induced covalent damage is misrepaired, altering the base sequence from the original. Alternatively, undetected covalent damage that is not repaired prior to DNA replication could induce a misread by DNA polymerase, causing a base substitution that alters the original sequence. Indeed as UVR is responsible for so many cutaneous neoplasms, the National Toxicology Program has agreed to add exposure to UVR to its listing of known and suspected carcinogens.

Broad Spectrum Sunscreens – UVA Sunscreens

While the deleterious health effects of UVB are well known, a growing body of indirect evidence suggests a relatively greater role for ultraviolet A (UVA) in chronic sun damage rather than in acute effects such as sunburn, tanning, and vitamin D synthesis. UVA has several unique characteristics that make it a suspect in chronic sun damage – it constitutes 5.0% of the terrestrial profile of sunlight, UVA is 20-fold more abundant at the earth's surface than UVB; it is not filtered by window glass; it has little temporal flux attenuation; it is relatively unaffected by altitude and atmospheric conductions; and it has deep cutaneous penetration. Also, it has been shown that UVA radiation causes oxidative damage to guanine bases in DNA indirectly, through the creation of free radicals.

Given this growing body of evidence, the Academy was concerned that the Food and Drug Administration had failed to develop a standard for UVA protection in sunscreens in its final monograph published in May 1999. Because of these concerns, the Academy created a UVA Sunscreen Working Group in the spring of 1999 to examine the issue. After an examination of the issues and finding a lack of consensus on testing for an UVA protection factor, the UVA Sunscreen Working Group recommended that the Academy sponsor a consensus conference to provide a forum for discussion on this topic.

On February 4, 2000, a full-day consensus conference was held in Washington, DC. Meeting participants included members of the Academy, federal agencies (FDA, Environmental Protection Agency), representatives from the US, UK and European cosmetic and pharmaceutical industry, and representatives from the photobiological community. The goals of the conference, as outlined by the Working Group, included the creation of an open dialogue among members of the medical and scientific communities, industry and government; a presentation and discussion of the available *in vitro* and *in vivo* methods of UVA sunscreen protection determination; the development of a consensus on consumer labeling of UVA sunscreen protection; and the development of a listing of recommendations to the FDA regarding methods of assessment and labeling of sunscreens.

Following the presentation by leading scientists of the currently available *in vitro* and *in vivo* testing measures, conferees participated in discussion break-out groups to explore specific questions regarding UVA sunscreen protection determination methods and labeling. Following the conference, members of the Working Group further discussed these recommendations.

The following are the final recommendations for UVA protection of sunscreens of the American Academy of Dermatology. The Academy's Board of Directors at its most recent meeting in Nashville, Tennessee approved these recommendations.

1. Sunscreen UVB protection, as reflected by the SPF, should be the primary consideration for sunscreen policy.

2. *In vitro* critical wavelength method is a criterion for a broad-spectrum claim. The threshold for this claim should be 370 nm.

3. The critical wavelength method must be combined with an *in vivo* method; the latter could be either persistent pigment darkening (PPD), or protection factor in the UVA (PFA). A minimum of 4-fold *increase* in PPD or PFA value in the presence of sunscreen is recommended.

4. Only sunscreens that fulfill the above *in vitro* and *in vivo* criteria could be labeled as "broad spectrum."

5. No sunscreen, which has only UVA protection, may claim to be a "broad spectrum" sunscreen.

6. An increase in the SPF must be accompanied by a proportional increase in the UVA protection value. It is recommended that these "proportional" values be determined jointly by the FDA and industry.

7. A threshold, pass/fail labeling for broad spectrum/UVA protection is recommended. Therefore, sunscreens fulfilling the above criteria would be labeled simply as "broad spectrum." This would minimize confusion to the consumers. The specifics of the threshold (critical wavelength, PPD/PFA value, and the UVA/UVB proportionality) could be displayed in fine print on the back of the container.

8. More funding should be provided for radiation biology research to help elucidate UVA mechanisms of injury.

A copy of the proceedings from this conference is attached to this document.

SPF Cap of 30+

The Academy remains concerned of the agency's continued support of efforts to limit SPF values on sunscreen above 30 to one collective term of 30+. The Academy's objects to this continued approach for several reasons: it fails to recognize that most consumers fail to achieve the SPF as listed on the bottle, because they apply too little sunscreen; the directive fails to serve individuals at high risk, who may need a sunscreen with a higher SPF; and the directive will discourage industry from manufacturing better sunscreens.

The agency contends that the availability of high SPF sunscreens could encourage individuals to stay out in the sun longer and would "dilute" the desired public health message. The Academy disagrees. The united public health message of the Academy, the American Cancer Society, The Skin Cancer Foundation and other groups has not changed since the development of sunscreens with an SPF of 15 or higher. One might argue that those individuals who are practicing unwise sun habits would do so anyway. Furthermore, the need for high SPF sunscreens for individuals at high risk is a compelling argument for their availability.

Unfortunately, many of our patients apply too little sunscreen to infrequently to achieve the full SPF that is listed on the bottle. The "final" monograph, published in the early summer of 1999, requires that the label on a sunscreen instruct the consumer to apply the lotion or cream "liberally" or "generously." The Academy has previously indicated our concerns with language, and has urged the FDA to adopt requirements for more explicit application of the sunscreen. We also believe that consumer failure to apply the amount of sunscreen necessary to achieve the SPF rating contained on the label is an argument in support of higher SPF sunscreens.

Heretofore, the FDA has approached sunscreen as solely a means to prevent sunburn. This approach fails to acknowledge that sunscreen is an important tool in preventing skin cancer and is useful in protecting individuals from other harmful effects from UVR. Indeed, the Academy believes that narrow approach does not protect the public, but limits the public's ability to choose the product that best suits their needs. Limiting choice will also do harm to many individuals at high risk. These may include individuals at genetic risk for the development of skin cancer, individuals who are immune-suppressed, individuals with outdoor occupations or who will have a high cumulative UV exposure, individuals who desire minimal photoaging, and individuals with photosensitivities.

Genetic susceptibility is recognized as a risk factor in the development of many kinds of cancer, including skin cancer. In recent years, scientists have identified the gene associated with melanoma (p16 gene); nevoid basal cell carcinoma (PTC); and most recently researchers at the University of California at San Francisco discovered that the *ptch+/-* mouse has an alteration in the tumor suppressor gene that allows the mice to

develop a high incidence of basal cell carcinoma-like tumors in response to chronic UVR exposure or a single dose of ionizing radiation. Also, individuals with Xeroderma Pigmentosum, a genetically determined photosensitivity disorder, are at high risk for developing skin cancer. Individuals with these mutated genes are at a higher risk for developing skin cancer than the general population when exposed to UVR. Sunscreens with a high SPF are needed to provide added protection to these individuals.

The skin is the largest organ of our immune system. A growing body of evidence suggests that UVR exposure has a deleterious effect on our body's ability to fight disease. Measurable effects of UV exposure on the immune system include the suppression of cutaneous responses to topically applied antigens and the development of unresponsiveness. Furthermore, individuals on immune-suppressive therapies, such as transplantation patients, have an enhanced risk for skin cancer, especially those with excessive sun exposure prior to transplantation or for those patients who continue sun exposure after transplantation. Transplantation patients would benefit from the availability of a high SPF, broad-spectrum sunscreen.

Individuals who have chronic UVR exposure as a result of their occupation would benefit from the availability of high SPF sunscreens. Individuals in the construction trades, farming, life guarding and other occupations that require work out of doors would benefit from the availability of high SPF, broad spectrum sunscreens, as regular use of these sunscreens could theoretically reduce lifetime UV exposure.

Many of the cutaneous signs associated with aging, such as wrinkling, are due largely to solar exposure and are theoretically preventable. Protecting individuals from photoaging is more difficult than sunburn prevention.

In photoaging, both UVA and UVB contribute to photoinduced damage such as oxidative damage and erythema. As mentioned above UVA has several unique characteristics that make it a suspect in chronic sun damage and photoaging. Photoinduced changes in the dermis may be involved in the formation of wrinkles that accompany aging. UVR effects on cytokine release and signal transduction pathways may alter expression of enzymes that remodel the dermis. Quantitative and qualitative changes in dermal macromolecules such as collagen, glycosaminoglycans and elastic fibers follow exposure to UVR. Sunscreens with a higher SPF and with broad-spectrum protection against UVB will help in both preventing photoaging and in repairing it. Research has shown that use of sunscreens shifts the balance of tissue remodeling toward net repair by preventing additional deposition of abnormal ground substance.

UVR can have deleterious health effects on individuals with cutaneous diseases other than skin cancer. These photosensitivity disorders include a wide range of clinical entities, and can include some disorders that are relatively common and others that are

exceedingly rare. Patients with polymorphous light eruption (PMLE) have inflammatory skin lesions primarily on the arms and upper trunk. PMLE is a relatively common disorder, occurring in 10-20% of otherwise healthy individuals. Exposure to both UVB and UVA rays can trigger PMLE, as can visible light. Given the broad action spectrum for this disorder, it is understandable that the limited number of formulations of sunscreen available in this country has not been very useful for PMLE patients. An abstract at the 1999 annual meeting of the Academy showed for the first time that very high SPF (greater than SPF 60), very broad-spectrum sunscreens may be useful in ameliorating this disease.

In addition to PMLE, UVB and UVA can play a role in the induction of lupus erythematosis, suggesting that oxidative damage may play an important role in this disease. One model suggests that the release of proinflammatory cytokines may trigger the appearance of pathogenic cellular antigens on the surface of skin cells. Photosensitivity is a common manifestation of both systemic and cutaneous lupus. Photosensitivity is correlated with a less favorable prognosis and more organ involvement in systemic lupus and exacerbations of cutaneous lupus. Photoprotection measures, such as the use of high SPF, broad-spectrum sunscreens have proved useful for patients with lupus, but as with PMLE, the sunscreens currently available in the U.S. are inadequate to the task.

And what will be the incentive for industry to work hard to develop a high SPF, broad-spectrum sunscreen in the U.S.? If the language in the monograph is allowed to stand, industry will have no incentive to meet this goal. Indeed, patients with special needs, such as a lupus patient, will be unable to determine from the label whether her sunscreen will be able to protect her from photosensitivity reactions. Furthermore, the limited number of formulations currently permitted under the monograph does not provide us with broad-spectrum protections at low levels of SPF. Therefore, in order to ensure that a sunscreen is protective against the damage of UVA rays, the consumer should purchase a sunscreen with a high SPF.

Adoption of the COLIPA Standard and Other Testing Issues

The proposed final rule requests comments on the adoption of a spectral power distribution that specifies the proportion of erythema-effective radiation in a table format and that the FDA replace the specifications currently in force with that of the European Cosmetic, Toiletry and Perfumery Association or COLIPA standard.

A standardized source of UVR for determining the SPF levels of sunscreens would be helpful, as it could ameliorate the FDA's stated concern with the interlaboratory variation in SPF testing methodology. However, as the Academy has indicated its support for both *in vitro* and *in vivo* testing of sunscreens to determine if the formulation provides broad-spectrum coverage, reliance on only a solar simulator for testing would be impractical. Use of a high intensity UVA source in the UVA

photoprotection test would reduce the amount of exposure time to the light source for testing volunteers.

In any event, the Academy encourages the FDA to work closely with industry to develop a standard that is practical, affordable and acceptable to both parties.

I hope that these comments will be helpful to the FDA in its efforts to finalize the monograph. If the agency would like any additional information on these comments, the Academy would be pleased to provide it.

Sincerely,

Richard Scher

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President

rs/cah

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By Messenger